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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/092,297	06/05/1998	PATRICIA A. BILLING-MEDEL	6107.US.P1-0	5922

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/092,297	BILLING-MEDEL ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16,25,30,33,35 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25, 38* is/are allowed.

6)☒ Claim(s) *10-16,30,33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 10-16, 25, 30, 33, 35, 38 are pending and under consideration.

Response to Amendment

The rejections of now cancelled claims 33, 39 and 45-55 have been rendered moot and are thus withdrawn.

The Objections to the claims have been withdrawn based on Applicant's amendment.

The Objection to the Specification has been withdrawn based on Applicant's amendment.

The rejection of pending claims 10-16, 25, 30, 33, 35, 38 under 35 USC § 112 first paragraph as lacking enablement for a polynucleotide 90-095% identical to SEQ ID NOs: 5, 17 has been withdrawn based on Applicant's amendment.

The rejection of pending claims 10-16, 25, 30, 33, 35, 38 under 35 USC § 112 first paragraph as lacking written description for a polynucleotide 90-95% identical to SEQ ID NOs: 5, 17 has been withdrawn based on Applicant's amendment.

The rejection of claims 25, 30 and 38 under 35 USC § 112 second paragraph have been obviated by Applicant's amendment and are thus withdrawn.

Remaining issues, and new issues are set forth below.

Priority

The filing date of claims 10-16, 25, 30, 33, 35, 38 is deemed to be the filing date of the instant applications, i.e. 6/05/1998, as the parent application does not support the claimed limitations of the instant application.

As set forth in the Office Action of 6/3/2003, the parent application fails to provide written support for instant SEQ ID NO: 5, since the sequence in the parent application, i.e. SEQ ID NO: 3 differs at 3 nucleic acid positions from the polynucleotide sequence of SEQ ID NO: 5 in the instant application. Applicant argues that parent sequence SEQ ID NO: 3 uses the notation "N" at those three positions, and according to the IUPAC-IUB definition for the use of the "N" notation, that encompasses all four nucleotides, and thus there is written description for the polynucleotide of SEQ ID NO: 5 in the parent application. However, an award of priority cannot be made to a partial sequence in the parent application, as the addition of the defined nucleotides constitutes new matter. If the sequences were the same there would be no need for a different sequence identifier. As set forth in MPEP § 201.08 when the priority date is need to overcome an intervening reference the Office the earlier nonprovisional application discloses the invention of the second application in, the Examiner has to determine whether the earlier nonprovisional application discloses the invention of the second application in the manner provided by the first paragraph of 35 U.S.C. 112. Here the requirements of 35 USC 112 first paragraph are not met because disclosure of an "N" in the parent fails to provide a written description of the instantly claimed sequence. The priority date awarded for the claims is the filing date of the instant application, 6/5/1998.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-16, 33, 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which is enabling for a full length BL172 protein of SEQ ID NO: 5 and 17, does not reasonably provide enablement for a sequences which are complementary to SEQ ID NO: 5, 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims as written encompass polynucleotide sequences complementary to SEQ ID NO: 5 and 17. The scope of these claims are overly broad since insufficient guidance is provided as to which of the myriad of variant polynucleotides encode polypeptides which will retain the characteristics of BL172. The claims are directed to variant polynucleotides encoding polypeptides, and the term BL172 itself encompasses variant proteins. However, Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of BL172. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, As an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the

G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving ride to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In the instant case the claims do not set forth a limitation setting forth a function which the polynucleotides or encoded polypeptide must possess, and the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements

of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for polypeptide variants of BL172, and has not taught how to make polypeptide variants of BL172, it would require undue experimentation of one of skill in the art to make and use the claimed polypeptides.

Claims 10-16, 33, 35 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims as written encompass polynucleotide sequences complementary to SEQ ID NO: 5 and 17. The specification and claim do not indicate what

distinguishing attributes shared by the members of the genus. The specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the BL172 variants. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 5, 17 are insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information

regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and encoded polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an host cell in culture comprising a polynucleotide with the sequence as set forth in SEQ ID NO: 5, 17, or an isolated host cell comprising a polynucleotide of a sequence as set forth in SEQ ID NO: 5, 17 does not reasonably provide enablement for in vivo transfection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification on page 45 discloses that the nucleic acids of the current invention can be expressed in a wide variety of host cell types, and the definition includes cells within a host animal. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 5 or 17 in an animal. As is commonly known in the art, the transfection of cells within an animal with foreign nucleotide

sequences is fraught with difficulty, and is complicated by many variables, including among others, the method of delivery of the polynucleotide, the appropriate vector which comprises the polynucleotide of interest, and continued expression of the polynucleotide within the host cells. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, therefore, the claims as written are not enabled. The instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, therefore, the claims as written are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-14, 33, 35 stand rejected under 35 U.S.C. 102(b) as being anticipated by and also on sale and publicly used from Boehringer Mannheim Biochemical , 1991 catalog, page 557, for reasons of record set forth in the Office Action of 6/3/2003.

The claims are drawn to test kits and isolated polynucleotides that are complements. Boehringer teaches and sells random hexamer primers that are complements to all nucleic acid sequences and which is available in a container. The claims are anticipated in that the claims encompass "complements" of the claimed nucleotide sequence, i.e. SEQ ID NO: 5, but do not include a length limitation for the complementary strand. Thus the random hexamers meet the limitations of the claims and the claims are anticipated.

Claims 11-16, 33, are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9315197 (Stanchi et al).

Stanchi et al. teaches the cloning and expression of osteogenic protein-1 (OP-1). The nucleic acid that encodes the OP-1 protein comprises complements of SEQ ID NO: 5 (See Sequence Comparison A, attached). The Stanchi et al. reference further teaches the cloning of this polynucleotide into a vector, and transfection into host cells, and it is an inherent property of this polynucleotide to encode an epitope, thus claims 11-16 are anticipated.

Claims 10-14, 33, 35 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al, EST Database Accession No. AA195677 alignment, 19 May, 1997.

Claims 10-14, 33, 35 are drawn to polynucleotide sequences which are complementary to SEQ ID NO:5. The claims are anticipated in that the claims encompass "complements" of the claimed nucleotide sequence, i.e. SEQ ID NO: 5, but do not include a length limitation for the complementary strand. Thus the polynucleotides taught by Hillier et al. meets the limitations of the claims and the claims are anticipated.

Applicants argue that they are entitled to their priority date and that the 1.131 declaration supercedes the reference. Applicants response has been fully considered but is not persuasive because as set forth above there is no basis for priority to the sequences now claimed and further a 1O2(b) may not be obviated by a declaration. Thus, the rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-16, 33, 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 9315197 (Stanchi et al), and further in view of the Stratagene catalog (1988, page 39).

Stanchi et al. teaches the cloning and expression of osteogenic protein-1 (OP-1). The nucleic acid that encodes the OP-1 protein comprises complements of SEQ ID NO: 5 (See Sequence Comparison A, attached). The Stanchi et al. reference further teaches the cloning of this polynucleotide into a vector, and transfection into host cells, and it is an inherent property of this polynucleotide to encode an epitope. The Stanchi et al. reference does not teach the use of a kit. The Stratagene catalog does teach a motivation to combine reagents of use into a kit page 39, column 1). IT would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the labeled nucleic acid molecule as taught by Stanchi et al. in combination with Inagaki et al into a kit as taught by Stratagene since the Stratagene catalog teaches a motivation for combining reagents of use in any assay into a kit. It states that "Each kit provides two services: 1) a variety of different regents have been assembled and premixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 1 different reagents, each of which is needed in only microgram amounts, when

beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

Claims 10-16, 33, 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hillier et al, EST Database Accession No. AA195677 alignment, 19 May, 1997 in view of Expression of Cloned Genes in E. coli, Sambrook et al, Cold Spring Harbor Laboratory , 1989.

Claims 10-14, 33, 35 are drawn to polynucleotide sequences which are complementary to SEQ ID NO:5. The claims are anticipated in that the claims encompass "complements" of the claimed nucleotide sequence, i.e. SEQ ID NO: 5, but do not include a length limitation for the complementary strand. However Hillier et al does not expressly teach a transfected host cell and a method of producing the polypeptide fragments using the host cell transfected with the polynucleotide fragments. Sambrook et al teach the expression of polypeptide fragments from cloned DNA sequences, using the DNA sequence, a vector and host cells transformed with the vector. Given the teachings of Sambrook et al it would have been prima facie obvious for one of skill in the art knowing the DNA sequence of Hillier and the techniques of Sambrook to insert the DNA sequence into an expression vector, transfect host cells and produce the polynucleotides

and polypeptides as claimed. One of skill in the art would have been motivated to do so based on the ease and effectiveness taught by Sambrook et al for obtaining abundantly produced polypeptides for use in further analysis of the particular proteins properties and functional characteristics and would have expected success given the high skill in the art. Applicants argue that they are entitled to their priority date and that the 1.131 declaration supercedes the reference. Applicants response has been fully considered but is not persuasive because as Applicants argue that they are entitled to their priority date and that the 1.131 declaration supercedes the reference. Applicants response has been fully considered but is not persuasive because as set forth above there is no basis for priority to the sequences now claimed and further a 102(b) may not be obviated by a declaration. Thus, the rejection is maintained for the reasons of record.

Conclusion

Claims 25 and 38 are allowable.

Claims 10-16, 30, 33, 35 are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1646
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